A CONTRIBUTION

TO THE

HISTORY OF LEUCEMIA

(INTESTINAL LEUCEMIA)

BY

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The researches of Professors Bennett and Virchow, and the ulterior investigations of several other observers, have established beyond a doubt the existence of two distinct varieties of Leucemia or Leucocythemia.

The first of these is generally known under the name of *splenic Leucemia*. Its leading characteristics (apart from the low cachectic state of the patient) are, a considerable hypertrophy of the spleen, which is often found to be twice or three times larger than in the healthy state (or even more); and the presence, in the blood, of an increased number of white globules. Instead of standing in the proportion of *one* to 360 red globules, they multiply to such a degree, that sometimes the blood, when examined under the microscope, appears to contain an equal number of both white and red corpuscles.

In this form of Leucemia, the white globules are large and fully developed, as well as more numerous than in the normal state; and their dimensions are much greater than

in the second variety, of which we shall presently have to speak.

In *splenic* Leucemia, as may be inferred from the name of the disease, the spleen is the seat of important alterations, while the lymphatic ganglia appear to undergo no morbid change whatever, unless, indeed, they happen to be slightly enlarged, which does not always occur.

The cases of this kind are by far the most numerous; I have met with several this very year, in the clinical wards of La Pitié. One of these patients died, with a vast effusion of blood in the cellular tissue, under the right scapulum.

In the second variety of Leucemia, which is by far less frequent than the first, the cachectic state of the patient remains the same, but the spleen does not exhibit any morbid increase of size; while the lymphatic ganglia, in various regions, grow enormously large; and the blood, when examined under the microscope, is found to contain enormous proportions of white blood-cells : but, their size, in this form of the disease, is much smaller than in splenic Leucemia; and their general appearance closely resembles that of lymph-corpuscles.

This second variety has in general been viewed as closely connected with the exaggerated development of the lymphatic ganglia : it has therefore been designated under the name of *adenoid* or *lymphatic* Leucemia.

A frequent complication of both these forms of the disease, as noted by various authors whose attention has lately been drawn to this subject, is the formation of deposits of lymph-corpuscles, in the liver, the kidneys, the mucous coat of the stomach and intestinal tube, and the pleura. Professors Virchow, Friedreich and Bottcher, have recorded several cases in point; the fact has more than once

been noticed at Paris, and I have lately heard of a case in which a similar deposit had been formed in the stomach, and in consequence of the cachectic state of the patient, had, at first, been mistaken for cancer.

But, up to the present time, these lymphatic deposits had only been met with in patients, whose spleen, or lymphatic ganglia were already the seat of a morbid process.

In the clinical service at La Pitié, with which I am at present intrusted, I have lately met with a case of Leucemia, which differs from those I have just mentioned, and offers, in my opinion, a certain importance in a scientific point of view : in fact, it establishes the existence of a new variety of the disease, which hitherto had not been described, and completes the list of morbid alterations, which the lymphatic system undergoes in Leucemia ; it may, perhaps, also throw some light on certain points connected with the study of other diseases.

This meeting, Gentlemen, will, at all events, be fully prepared to form a correct judgment on this point, after hearing the facts of the case, and examining the anatomical pieces and histological preparations which I now place before you.

The following is the history of the case.

Foubert, a warehouseman, aged 25, was admitted, on the 19th of June 1868, into the wards of Dr Gallard at La Pitié, and was transferred a month later to the clinical service (July 17th).

The patient states that up to the beginning of April 1868, he enjoyed a perfect state of health, with the exception of a slight indisposition which occurred when he was 13 years of age, and which may perhaps have been an attack of intermittent fever, although this point is doubtful. He positively affirms, that the village in which he lived is free from any similar complaint. At all events, it is quite certain that his illness did not last long,

and that for the last 12 years he has not experienced one moment's illness. During childhood, he never suffered from enlargement of the ganglia, in the neck or in other parts; and no scars are to be met with in any region of the body.

His father and mother are in good health, as well as a brother and a sister who live in the country.

The patient came to Paris in 1864, and has since then been constantly employed in the same warehouse; he was often obliged to carry large and heavy parcels to a great distance, and felt often severely tired with his day's work. He slept in a spacious, well aired, and perfectly dry room. His diet was wholesome; he used to drink about half a bottle of wine a day; and, in all respects, his habits were perfectly regular. He never contracted any syphilitic taint; and, in a word, his health remained excellent till April 1868. Up to that date, he positively affirms that he was strong, ruddy, and in good condition; and, according to his own expressions, " he was not afraid of work. "

In the month of April of the present year, he began to feel that his strength was gradually diminishing, that he easily got tired, and that his face was growing pale. Any extraordinary exertion gave rise to violent palpitations, and brought on dyspnæa for several minutes. He was also gradually growing thin, although no sudden change had taken place in this respect.

The patient's appetite, however, remained pretty good; there was no diarrhæa, but, on the contrary, a certain degree of costiveness. No loss of blood had taken place either from the nose, from the gums (which were perfectly sound), nor from the anus; (there existed no hæmorrhoidal tumour.) There was no vomiting, and the digestive functions were regular. No pain whatever was felt either in the head, the chest, or the abdomen.

The sexual propensities had considerably diminished since the beginning of the disease.

These symptoms continued to increase gradually, without any sudden aggravation. The patient continued to work, u t

with great difficulty. Towards the end of May, he became unable to walk to any distance, and grew so pale, that his friends noticed his singular appearance, and called his attention to the fact. No other morbid symptoms had made their appearance; neither vomiting, nor diarrhæa, nor coughing, nor perspiration, nor hæmorrhage from any point.

On the 19th of June, feeling altogether incapable of continuing his daily labour, he entered Dr G.'s wards at La Pitié, and, on the 17th of the following month, was transferred to the clinical service, N° 7, salle Saint-Paul. We found him in the following condition :

The patient is a tall man, who appears to have enjoyed considerable muscular strength. He is at present excessively thin and pale; the whole surface of the body is of a yellowish white; the inner surface of the eye-lids has entirely lost its red colour, as well as the tongue and gums, which are not swollen, and do not bleed.

The heart is slighty enlarged : the præcordial dulness covers a space of six or seven square *centimètres* (about an inch and a half); its pulsations are feeble. No murmur is heard at the apex : the impulsion is weak; but, at the aortic orifice, a soft murmur coincides with the first sound, and is heard all along the aorta. A continuous anæmic murmur is perceived in the vessels of the neck. The jugular and subclavian veins, especially on the right side, exhibit strong pulsations, which coincide with the contractions of the heart, and may be considered as a *venous pulse*.

No enlargement of the spleen is found on percussion, although this point has been repeatedly examined with the greatest care.

The lymphatic ganglia, both in the axilla, and in the inguinal region, are of a moderate size, and no larger than they frequently are in emaciated and cachectic subjects. There is not the slightest appearance of morbid hypertrophy.

The blood, drawn from one of the fingers, has been more than once examined under the microscope, and has always exhibited

the same appearance. The red globules are considerably reduced in number; they are pale in colour, and irregulary agglomerated in small masses. A large quantity of white blood-cells, (almost as many as the red ones,) is found to exist; when examined with respect to their individual characteristics, they are found to be of moderate dimensions : they evidently belong to the *lymphatic* form of the disease, and are decidedly smaller than those of the *splenic* variety of Leucemia.

The patient's appetite has now almost entirely failed : his digestions are slow and laborious; but there is no vomiting. Pressure on the epigastric region is slightly painful. The stools are rather hard, and not very frequent. The abdomen is slightly tumefied, and gives a tympanic sound on percussion.

The urine is excreted without pain, and only a few times in the day : it exhibits no morbid colour, and contains neither albumen nor sugar.

Although neither percussion nor auscultation reveal any morbid state of the lungs, the respiration is irregular. The inspirations are short, and amount to thirty per minute. In spite of this, the skin is not particularly hot; the pulse, which is large and soft, stands at 80.

There has been no bleeding at the nose, no hæmorrhage on any point. There exists a slight frontal head-ache, and a little swelling round the instep : the upper part of the legs is, on the contrary, rather emaciated.

To resume the symptoms of the case, the patient, during two months and a half, had been losing strength, and growing pale, although he did not appear to be under the influence of any debilitating process; neither diarrhæa, nor vomiting, nor loss of blood. Besides, although neither the spleen, nor the lymphatic glands were enlarged, the blood contained a very large quantity of white cells, of small dimensions, and belonging to the *lymphatic* or *ganglionic* variety of the disease.

This state of the blood, although strongly marked, ap-

peared singular enough, when neither the alteration of the spleen, nor those of the lymphatic ganglia, which usually attend Leucemia, could be discovered : and the *organic* cause of the disease entirely escaped our investigation.

PRESCRIPTION (1) :

Vin de quinquina.....	200 gr. (7 ounces)
Vin de Bagnols.....	200
Extrait de quinquina.....	2

Morning and evening.

Two of Petrequin's pills daily (2).

In spite of this treatment, corroborated by a tonic diet, the patient continued to sink rapidly : the remedies administered remained powerless, and the intense summer heats, which have lately prevailed, brought on profuse perspiration. At last he expired, without any acute symptoms, on the 22d of July, at four P. M.

Post mortem, performed twenty-four hours after death.

Viewed externally, the body is exceedingly pale and emaciated.

Thorax. Superficial pleural adhesions, which unite the right lung to the walls of the chest. A small quantity of a light yellow fluid exists on this side, without any pseudomembranous concretions.

Lungs perfectly sound, without any induration, but colourless; on pressure, no blood oozes from their tissue.

(1) We have not attempted to translate the prescription into English, as the preparations of the French Codex do not correspond to those of the British Pharmacopœia.

(2) The following is the composition of Petrequin's pills :

Sulphate of iron.....	8 gram. (120 grains)
Sulphate of manganese.....	2
Bicarbonate of soda.....	10
Honey.....	q. s.

For 80 pills.

Pericardium containing a certain quantity of a transparent liquid. No adhesions.

Heart enlarged (about two thirds of its normal size). Left cavities empty; right cavities filled with yellowish, soft, gelatinous clots. The mitral valve is sound; the sigmoid valves of the aorta appear insufficient when water is poured upon them; but they do not exhibit any morbid alteration in their texture.

The *liver* is neither smaller nor larger than in the normal state; its tissue is sound, but discoloured; the *cystis fellea* contains a small quantity of a light-yellow fluid.

The *pancreas*, carefully examined, is found to be perfectly normal.

No morbid alteration in the *suprarenal capsules*.

The *left kidney* is anæmic, but exhibiting no alteration in size, shape or texture.

The *right kidney*, although unchanged in size and shape, is evidently the seat of fatty degeneration.

The *spleen* is but little larger than in the normal state. Its section is of a rosy white colour. Its consistency is firm, and its surface when scraped gives little splenic matter. This peculiar *hardness* had led us at first to suppose that there existed an amyloid degeneration; but the chemical reagents employed (iodine, sulphuric acid) showed no signs of this peculiar alteration.

The *inguinal and axillary ganglia* are very small, and rather hard, but without any morbid change. The *mesenteric ganglia* are about the size of a little hazel-nut; they are hard, and of a rosy colour.

The *digestive tube*, however, examined in all its parts, presents considerable and interesting morbid alterations.

The *stomach* is perfectly sound; but the whole extent of the lesser intestines is completely anæmic. The surface of the *peritonæum* is in a healthy state.

Examined with the naked eye, the *mucous coat of the intestines* exhibits the following lesions :—

The whole surface is of a greyish colour, with a granular

appearance, which, on closer inspection, is found to result from a deposit of pigment at the apex of the villosities.

The Peyerian patches, wherever they exist, especially in the vicinity of the ileo-cœcal valve, are thicker and more prominent than in the normal state. On certain points, they are so visibly increased in size, that they seem not only thicker, but even broader than in the normal state.

No ulcerations are to be seen on the surface of these patches, notwithstanding all the care which has been bestowed on this point. Their surface rises about three millimetres (1/8th of an inch) above the surface of the mucous membrane, which is swollen, and offers a reticular appearance, and contains pigment deposits. The annexed drawing gives an idea of their appearance in a fresh state.

The thickness of these patches is shown not only by their prominence, but also by their opacity; when the intestinal tube is held up against the light, its transparency is visibly diminished in the corresponding points; there exists a striking contrast, in this respect, between the opacity of Peyer's patches, and the transparency of the remaining parts of the intestinal tube, which is anæmic, and seems thinner than usual.

The solitary glands are prominent both in the small and large intestines : they are of a dull white colour, and about the size of a millet-seed. They appear quite opaque, when the intestine is held up to the light. The follicles of the large intestine are voluminous, prominent, white and *non-transparent*, like those of the small intestine.

None of these glands are ulcerated, in any part of the intestinal tube.

The histological examination of these organs has been preceded by their immersion in pure alcohol; the patches and solitary glands have therefore become still more prominent than in the fresh state, while the whole preparation has grown much harder than in the fresh state.

Peyer's patches. When one of the larger patches is closely

examined after being plunged in alcohol, a perpendicular section exhibits all the successive layers which compose the walls of the intestinal tube.

The serous and muscular membranes are sound. The cellular tunic is slightly thicker than in the natural state; and under it is placed an opaque, whitish layer, about three millimetres in thickness, which fills up the place of the mucous coat, and stands in contact with this latter membrane by its circumference; the villosities are normal, on the mucous surface, while those which correspond to these white layers are considerably altered from the healthy state.

When this diseased portion is held up to the light, and examined with the naked eye, or with a magnifying power of twenty diameters, two remarkable features are observed :

1° The villosities which lie on the surface are hypertrophied, and much longer than usual : they are less transparent than the sound ones which correspond to the healthy parts of the mucous coat.

2° Under these, a series of circular lacunæ is observed : their circumference is slightly irregular; they are disposed in a line which runs parallel to the surface. These lacunæ are produced by the disappearance of the intestinal glands, which have fallen out of their places at the moment when the preparation was made. In fact, in the unequal intervals which separate these lacunæ, a certain number of opaque spots are found; these are precisely the follicles which remained in the intestinal tissue, when the others fell out.

In order to ascertain the composition of the tissue which produces this superficial induration of Peyer's patches, a thin section being made and deposited on a glass slide, is gently struck with the extremity of a camel's hair pencil, in order to separate the tissues and allow them to be viewed apart. The preparation is then coloured with a solution of carmine in ammonia, washed in water, and touched with acetic acid. It then becomes easy to see that the thickened portion of the patches

is formed by a lymphatic deposit or *lymphoma*. In fact, a reticulum formed by minute fibres, which anastomose with each other, is found to exist; little nodosities correspond to these inosculations, and the trabeculæ adhere to the walls of an infinite quantity of capillary vessels, which circulate in the deposit. The meshes of the reticulum are filled up by a number of little round cells, containing a nucleus which almost entirely fills up their capacity. The nature of these elements, and the disposition of the reticulum can easily be ascertained on the points where the Camel's hair pencil has dissociated the tissues, and set free a certain quantity of these little cells. But on the other points, where the reticulum has remained unaltered, the cellular elements are so numerous and so closely packed, that the reticular tissue is entirely concealed from sight.

In the midst of this lymphatic deposit, are situated the vesicular glands, which when united form one of Peyer's patches. When we examine the circumference of the above mentioned lacunæ, which, as we said before, are produced by the extrusion of the follicles at the moment when the microscopical section is made, we find the *reticulum* broken on this point, and several of the corresponding capillary vessels broken too; a disposition which shows the close connexion between the follicle and the lymphatic deposit which surrounds it.

The gland itself, when examined on the points where it has not been extruded, joins the ambiant tissues at its circumference : the opacity of the membrane, viewed with the naked eye, is greater under the follicle, than on other points. The tissue itself has undergone no fatty degeneration, nor any other morbid change. Its elements are *increased in number*, without any change of structure : their multiplication is the sole cause of the increased dimensions of the follicle itself.

The lymphatic deposit seems to have invaded the whole breadth of the mucous membrane, for there remain no vestiges of the tubular glands. The villosities are double or treble their natural size : their basis is broad, and unites with the lymphatic

deposit. When carefully examined, they are found to contain an abundance of cellular elements; but the granulations and fatty vesicles which fill the tissue itself leave some doubts as to the result, and do not allow us to affirm positively that the hypertrophy of the villosities is due to the lymphatic deposit, although this seems highly probable.

In concluding this description of Peyer's patches, we must state that the lower surface of the lymphatic deposit is distinctly limited, and does not join the cellular coat of the intestinal parietes. On this point, the cellular tunic is a little thicker than in the normal state, but more especially in the vicinity of the lymphatic deposit, and a great deal less on its outer surface.

And, lastly, this new lymphatic tissue exhibits no trace of fatty degeneration or other changes, the lymphatic elements being perfectly regular in their appearance.

Solitary glands A section perpendicular to the axis of the intestinal tube being drawn through the centre of one of these follicles, the following results are obtained :

1° In most cases, the gland escapes as before, leaving behind it a lacuna or cavity, like those which have been already described in Peyer's patches.

2° The circumference of these cavities is formed by a circular zone about half a millimetre in extent, which leans towards the sub-mucous coat, but is more prominent on the inner surface of the intestine.

3° On the lateral parts of this zone, it joins the mucous membrane, which is perfectly sound, and no thicker than usual, and is plentifully stored with tubular glands, and perfectly healthy villosities.

4° The villosities which correspond to the follicles are hypertrophied, like those of Peyer's patches : their broad basis rests upen, and unites with the newly formed tissue, which forms the peri-follicular zone.

5° All that has previously been said with respect to this new tissue, in the description of Peyer's patches, may be repeated

without the slightest variation here. This circular band is identical with the substance previously described, and is also the result of a lymphatic deposit.

The remaining parts of the intestinal mucous membrane are perfectly sound; the villosities and glands are quite healthy.

The morbid change, therefore, in the present case, entirely consists in lymphatic deposits, or lymphomata, which wholly occupy Peyer's patches and form a circular zone round the independent vesicular follicles.

We wish to call attention more specially to the fact, that the spleen was uninjured, and that the lymphatic ganglia were evidently sound; for the mesenteric glands themselves were of a moderate size, and the slight degree of enlargement which they exhibited was visibly occasioned by the morbid condition of Peyer's patchès. This case, therefore, is entirely different from those which have been placed on record by Professors Virchow, Friedreich and Bottcher, since the deposits observed in the intestinal tube were independent of all morbid alterations in the spleen or lymphatic ganglia.

If the foregoing description is a correct representation of facts, we stand in presence of an entirely new form of Leucemia, not only because the spleen and ganglia were free from all morbid changes, but also because the deposit was concentrated in the lymphatic organs of the intestinal tube—viz. Peyer's patches, and the solitary glands. This case, therefore, is an instance of *intestinal Leucemia*, without splenic or ganglionic lesions—a form of the disease which hitherto had escaped the notice of medical observers.

This variety of Leucemia, as I have already stated, completes the list of the lymphoid alterations which attend

this disease; a result which fully confirms the views maintained by Professor Virchow with respect to the nature of Peyer's patches and the solitary glands; both forming part, in his opinion, of the same general system as the spleen and lymphatic ganglia.

It may also be interesting to compare these chronic lesions of the patches, and solitary glands, giving rise to permanent Leucemia, with the acute disease which seizes upon the same organs in typhoid fever, and coincides with a momentary increase of the white blood-cells. Several writers, and particularly Professor Virchow, attribute this transient state of the blood to the exaggerated activity of Peyer's patches and the solitary glands, which, in typhoid fever, become ulcerated, after swelling to a considerable size. This doctrine has been clearly expounded in the remarkable work of my excellent friend Dr Murchison, *On the continued fevers of Great Britain* (p. 557). The case which I have placed on record brings additional strength to this opinion.

In fact, if there only exists a transient and momentary Leucemia in typhoid fever, it must be borne in mind, that the hypertrophy of Peyer's patches, with which this multiplication of the white globules seems to be connected, is also of a transitory nature, and is speedily succeeded by ulceration, which entirely suppresses their functional activity, or by resolution, which brings it back to the normal state.

On the contrary, in the present case, the morbid change is permanent, and assumes a chronic form; there is no tendency to ulceration or resolution, so that the excessive multiplication of the white blood-cells is permanent, as well as the hypertrophy of the lymphatic tissue; and thus

a positive lymphatic cachexia is produced, and death results from a special form of debilitation.

You therefore perceive, Gentlemen, that the case on which I have attempted to call the attention of the present meeting, may prove interesting, not only from its novelty and rarity, but also from the light which it throws upon other subjects. It may also lead us to attribute a higher physiological importance to the vesicular glands of the intestinal tube, whether solitary or agglomerated ; it seems to point to their influence as modificators of the blood, and may perhaps induce us to place them among the *hæmatopoietic* organs.

These considerations, Gentlemen, which seem to flow naturally from the history of the case which I have reported, will perhaps render it sufficiently interesting to deserve the attention of the present meeting. My purpose, however, has chiefly been to bring this new variety of Leucemia under your notice.

THE END.

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